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How and for whom does supportive adjustment to Multiple Sclerosis cognitive-

behavioural therapy work? A mediated moderation analysis

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1 **Abstract**

2 The supportive adjustment for multiple sclerosis (saMS) randomised controlled trial showed

3 cognitive behavioural therapy (CBT) reduced distress at 12-months compared to supportive

4 listening (SL). Larger changes in distress and functional impairment following CBT occurred

5 in participants with clinical distress at baseline. This secondary analysis investigates whether

6 CBT treatment effects occur through pre-defined CBT mechanisms of change in the total

7 cohort and clinically distressed subgroup. 94 participants were randomised to saMS CBT or

8 SL. Primary outcomes were distress and functional impairment (12 months). Mediators

9 included cognitive-behavioural variables at post-treatment (15 weeks). Structural equation

10 mediation and mediated-moderation models adjusting for baseline confounders assessed

11 mediation overall and by distress level. Significant mediation was found but only for those

12 with clinical distress at baseline. Illness acceptance (-0.20, -0.01 to -0.46) and reduced

13 embarrassment avoidance behaviours (-0.22, -0.02 to -0.58) mediated CBT's effect on

14 distress. Changes in beliefs about processing emotions (-0.19, -0.001 to -0.46) mediated

15 CBT's effect on functional impairment. saMS CBT had effects on distress and functional

16 impairment via some of the hypothesised mechanisms drawn from a theoretical model of

17 adjustment for MS but only among participants with clinical distress at baseline. Increasing

18 acceptance and emotional expression and decreasing embarrassment-avoidance improves

19 MS adjustment.

20

21 *Keywords:* Multiple Sclerosis, Mediation and mediated moderation analysis, Cognitive-

22 behavioural therapy, Randomised Clinical Trial, Distress, Functional Impairment

23

24

25

Introduction

27

28   Multiple sclerosis (MS) is a chronic neurological condition with an estimated global

29   prevalence of 2.3 million (Browne et al., 2014). Symptoms common to MS include: sensory

30   disturbances, impaired balance, altered cognition, loss of mobility, spasticity, incontinence,

31   pain, and fatigue (National Institute for Health and Care Excellence, 2014). MS can present

32   as one of three subtypes; relapsing remitting, primary progressive, or secondary

33   progressive. Approximately 85% of patients are initially diagnosed with relapsing remitting

34   MS - whereby inflammatory processes exacerbate symptoms followed by periods of

35   remission (full or partial). Most people with relapsing remitting MS will eventually be

36   diagnosed with secondary progressive MS - whereby symptoms and disability progress over

37   time with or without periods of inflammation. Lastly, around 15% are initially diagnosed

38   with primary progressive MS - whereby symptoms increase over time resulting in

39   accumulating levels of disability (Lublin et al., 2014).

40

41   The illness poses significant challenges including an unpredictable and uncertain

42   illness trajectory, and symptom and treatment burden. Fifteen years post diagnosis, 70% of

43   people with MS (pwMS) report difficulties with activities in daily living and 75% report being

44   unemployed (Hauser & Oksenberg, 2006). Depression and anxiety are common. A

45   systematic review of 58 studies of pwMS reported prevalence rates of 31% for depression

46   and 22% for anxiety (Boeschoten et al., 2016). Lifetime prevalence estimates for depression

47   in pwMS are as high as 50% (Siegert & Abernethy, 2005).

48

49   Few studies have examined the effectiveness of treatments for anxiety in MS (Butler,

50   Matcham, & Chalder, 2016); a recent meta-analysis of seven randomised controlled trials

51   (RCTs) reported moderate effects of cognitive-behavioural therapy (CBT) on depressive

52   symptoms (standardised mean difference = -0.61, 95% CI -0.96 to -0.26) (Hind et al., 2014).

53   However, it remains unclear how CBT brings about these improvements. One way to ensure

54   CBT meets the needs of pwMS specifically is to view depression and/or anxiety in MS in the

55   broader context of adjustment to the illness. We developed a theoretical model of

56   adjustment to MS based on a systematic review of 72 studies investigating correlates or

57   predictors of adjustment to MS (Dennison, Moss-Morris, & Chalder, 2009). Adjustment was

58   broadly defined as an outcome which includes distress (including depression and anxiety),

59   well-being, quality of life, and impact of MS on life roles. The model proposed that illness

60   related critical events such as diagnosis, relapse, onset of new symptoms, and progression

61   often trigger a state of disequilibrium and distress within the individual. Acute distress may

62   be considered normal in these contexts, but if distress is prolonged, extreme and/or the

63   impact of illness on life roles is disproportionate to the extent of the symptoms, the person

64   experiences ongoing disequilibrium, and may be considered poorly adjusted. A variety of

65   psychological factors can either exacerbate the distress/disequilibrium or redress the

66   balance (See Dennison et al., 2009). Some of the psychological factors highlighted in

67   Dennison et al's (2009) model include: the ability to positively re-appraise one's situation,

68   high levels of perceived social support, use of social support and using problem-focussed

69   coping strategies. These factors were associated with better psychological adjustment to

70   MS. In contrast, high perceived stress, coping with MS by avoidance, not having strategies in

71   place to manage both negative emotions and MS related uncertainty was associated with

72   poorer levels of psychological adjustment (Dennison et al., 2009).

73   A manualised CBT protocol for supportive adjustment to MS (saMS) was developed

74 based on Dennison et al's (2009) theoretical model. The manual written content and CBT

75 techniques were mapped onto the factors identified in the model as enhancing adjustment.

76 For example, active problem-solving skills were taught alongside methods to enhance illness

77 acceptance and access good social support. The intervention also focused on modifying

78 factors shown to be related to poor adjustment. This included exploring and reappraising

79 unhelpful thoughts related to their MS and high personal expectations, managing difficult

80 emotions, and reducing the impact of stress. Figure 1 – provides a worked example of how

81 cognitive responses to an illness event (increase in symptoms) may trigger a vicious cycle of

82 behavioural, emotional and physiological responses which maintains or increases distress.

83 The saMS protocol helps to identify and challenge some of these thoughts and encourages

84 more helpful behaviours such as more consistent rather than all or nothing behaviour. The

85 protocol also encourages people to see appropriate outlets for emotional distress rather

86 than feeling it is unacceptable to show these feelings. A more detailed description of the

87 intervention components and how these map on to the factors identified by Dennison et al's

88 (2009) model is presented in Supplementary Materials Appendix A.

89

90 **Figure 1: An example vicious cycle of distress in response to a MS related ritical event –**

91 **change in symptoms**

92   [INSERT FIGURE 1 HERE]

93   In a randomised controlled trial (RCT), eight sessions of saMS CBT delivered by a

94 nurse were compared against a matched active control arm consisting of eight nurse

95 delivered supportive listening (SL) sessions (Moss-Morris et al., 2013; Moss-Morris et al.,

96 2009). There were two primary outcomes: i) psychological distress and ii) functional

97   impairment. saMS CBT demonstrated a statistically significant greater effect on

98   psychological distress at post-treatment (15 weeks) and 12 months follow-up that SL, but no

99   statistically significant effect on functional impairment at either follow-up time point.

100   However, planned moderation analyses suggested that pwMS who were clinically distressed

101   at baseline (see methods below for how this was defined) showed greater reductions in

102   both distress and levels of functional impairment at post-treatment and at 12 months

103   follow-up. Thus, pwMS with high levels of baseline distress appeared to be benefiting more

104   from the saMS CBT treatment.

105

106   Whilst the saMS primary RCT provided insights as to which patients are most likely to

107   benefit from CBT, it did not provide information about how CBT led to greater

108   improvements or how the treatment might be enhanced. One way to refine and improve

109   psychological treatments is to understand in more detail how treatments exert their effects

110   on outcomes using mediation analysis. In line with model of adjustment to MS, we selected

111   key factors for testing using mediation analysis (Dennison et al., 2009). It was assumed that

112   saMS CBT would exert its treatment effects on both primary outcomes by decreasing pwMS'

113   use of unhelpful cognitive and behavioural coping responses to MS (e.g. avoidance because

114   of feeling embarrassed, catastrophizing about uncertain symptoms), whilst increasing their

115   ability to accept their MS, improve their sense of self-worth, and express their negative

116   emotions to others by altering beliefs about the acceptability of experiencing negative

117   emotions. These mechanisms of action were targeted in the saMS CBT treatment

118   intervention and measured in the trial as potential mediators because they demonstrated at

119   least some evidence of association with adjustment outcomes in the theoretical model of

120   adjustment to MS described above and summarized in Figure 2.

121   **Figure 2. Example mediator model with all mediators listed and distress as outcome**

122   [INSERT FIGURE 2 HERE]

123

124   When there are significant treatment effects, mediation analysis provides further

125   information about the pathways through which a treatment transmits its beneficial effects

126   to clinical outcomes (Dunn et al., 2015; Goldsmith et al., 2018b; MacKinnon & Luecken,

127   2008). Here mediation analysis could elucidate the mechanisms via which saMS CBT

128   influenced distress. When a treatment is ineffective, mediation analysis is equally useful in

129   exploring why this occurred. For example, in saMS it may show that CBT was ineffective in

130   improving functional impairment because (a) it had no effect on its postulated target

131   (mediator) or (b) the target (mediator) had no effect on the outcome, or perhaps both. Such

132   analyses can inform decisions about the need to explore alternative treatment approaches

133   and/or alternative treatment targets (mediators/causal pathways of action) (Dunn et al.,

134   2015; Goldsmith, Chalder, White, Sharpe, & Pickles, 2018a). Mediation analyses also allows

135   theoretical models of treatment mechanisms of action to be empirically tested and refined

136   (Dunn et al., 2015; Goldsmith et al., 2018a). Supplementary Materials - Appendix A lists the

137   theoretically informed mechanisms of action targeted by the saMS CBT intervention and

138   also the self-report measures used to assess whether a change in these hypothesised

139   mechanisms of action occurred (e.g. a paths). We also list each of the hypothesised

140   mediators assessed in this study, in Figure 2 to clarify how each hypothesised mechanism of

141   action was tested. Table 1 (see methods) also lists in detail the measures used to assess

142   each hypothesised mediatory mechanism of action. From here on in, when describing

143   mediation we will refer to them collectively as putative mediators instead of listing each

144   mediator separately.

145   It is also possible to study whether mediation of treatment effects might be

146   occurring in certain patients but not others using mediated moderation analyses (Muller,

147   Judd, & Yzerbyt, 2005). As the CBT effects in saMS were largest for the those who were

148   clinically distressed at baseline, we also performed a mediated moderation analysis with

149   baseline distress as the moderator to examine if mediation effects differed depending on

150   whether pwMS were defined as meeting criteria for clinically meaningful distress or not.

151

152   **Research Questions**

153   The following research questions were addressed. Please refer to Figure 2, showing an

154   example single mediator model with acceptance as the mediator and distress as the

155   outcome:

156

157   1. Does saMS CBT significantly affect proposed mediators at 15 weeks follow-up when

158   compared with SL (*is the treatment - mediator relationship or a path significant?*)?

159

160   2. Which 15 weeks measures of the putative mediators are associated with

161   psychological distress and functional impairment at 12 months (*is the mediator -*

162   *outcome relationship or b path significant*)?

163

164   3. How much of the effect of saMS CBT on outcomes (psychological distress and

165   functional impairment) is transmitted via the mediators in the total sample (*Is the*

166   *indirect/mediated effect = a x b significant*)?

167   4. How much of the effect of saMS CBT on outcomes is transmitted via the mediators in

168   the groups that were defined as clinically distressed at baseline versus not clinically

169   distressed at baseline (are mediated effects moderated by baseline distress)?

170

171   **Methods**

172   This is a secondary mediation analysis of the saMS RCT using the RCT primary

173   outcomes and putative mediator variables measured as part of the study (Moss-Morris et

174   al., 2013; Moss-Morris et al., 2009).

175

176   **Participants & Design**

177   The RCT recruited and individually randomised 94 pwMS (diagnosed within the last

178   10 years). Full details of the trial inclusion and exclusion criteria and randomisation

179   procedures can be found in the trial protocol (Moss-Morris et al., 2009). The sample mean

180   age was 41.7 years (Standard Deviation, SD = 9.6) with a median time since diagnosis of

181   three years (range 0.8 to ten years). The majority had relapsing remitting MS (78%), 12

182   participants (12%) had primary progressive MS, whilst 10% had secondary progressive MS

183   (10%). A larger proportion of the sample were female (69%) and were of white British

184   ethnicity (76%). Forty-eight (51%) pwMS were randomised to saMS CBT and 46 (49%) to

185   supportive listening (SL) (Moss-Morris, 2013). Both interventions were delivered by nurses

186   over ten weeks. Both interventions included two face-to-face nurse therapy sessions and six

187   telephone sessions matched for contact time. The SL comparison arm of the trial was to

188   control for non-specific therapy factors (e.g. empathy and therapeutic alliance). The content

189   of the saMS manual is described in detail elsewhere (Moss-Morris et al., 2013; Moss-Morris

190   et al., 2009). The manual (Moss-Morris, Dennison, & Chalder, 2010) can be freely

191   downloaded from https://www.bl.uk/collection-items/supportive-adjustment-for-multiple-

192   sclerosis-sams-an-eightweek-cbt-programme-manualprotocol.

193

194   **Measures**

195   Self-report measures were collected at baseline, post therapy (15 weeks after

196   randomisation/post treatment), and 12 months follow-up (12 months post-randomisation).

197

198   **Primary Outcome Measures.**

199   The trial had two primary outcomes. The General Health Questionnaire (GHQ)

200   (Goldberg, 1992) measures symptoms of psychological distress over the past two weeks. It

201   is a twelve-item scale with a four-point Likert scoring system and is confirmed as a valid

202   measure of distress in pwMS. The GHQ can be continuously scored by summing each item in

203   the scale. High scores represent high levels of distress. Internal reliability as measured by

204   Cronbach's alpha was 0.91 at baseline and 12 months follow-up in our sample (Nicholl,

205   Lincoln, Francis, & Stephan, 2001). The GHQ can also be dichotomised using the 0011 GHQ-

206   12 scoring method, where answers of "more than usual" or "much more than usual" are

207   scored as 1 and other responses scored as 0 (Goldberg, 1992). As baseline, participants

208   were categorised as experiencing clinically meaningful levels of distress if they scored 3 or

209   above in total as recommended for MS (Lincoln et al., 2011; Moss-Morris et al., 2013;

210   Nicholl et al., 2001).

211

212   The Work and Social Adjustment Scale (WSAS) (Mundt, Marks, Shear, & Greist, 2002)

213   is measure of how much an illness interferes with the ability to work, engage with private

214   and social leisure activities as well as the degree to which relationships are impaired. It is a

215   widely used valid and reliable five-item scale with an eight-point Likert scoring system

216   Mundt et al. (2002). High scores represent high degrees of functional impairment. The

217   WSAS is scored by totalling all items in the scale. In this study pwMS were asked to rate

218   items in relation to MS interference. The Cronbach's alpha for the WSAS in our sample was

219   0.84 at baseline and 0.90 at 12 months follow-up.report high levels of validity.

220

221   **Potential meditators.**

222   Table 1 lists all of the mediators tested in this study and their psychometric

223   properties. Below we provide brief details about their reliability and validity.

224

225   Acceptance of MS was assessed using the Acceptance of Chronic Health Conditions

226   Scale (Stuifbergen et al., 2008). Data from 822 pwMS provided robust evidence for its

227   reliability and validity (Stuifbergen et al., 2008).

228

229   The psychological vulnerability scale (PVS) (Sinclair & Wallston, 1999) examines how

230   a person determines their sense of self-worth and whether this is dependent upon

231   achievement of goals Sinclair & Wallston (1999) confirmed the reliability and validity of the

232   PVS across three distinct samples of people with rheumatoid arthritis.

233

234   Unhelpful beliefs about emotions were assessed using the Beliefs about Emotions

235   Scale (BES)(Rimes & Chalder, 2010). The scale has demonstrated good reliability, validity and

236   sensitivity to change in response to treatment with CBT (Rimes & Chalder, 2010)

237

238   The Cognitive-Behavioural Responses to Symptoms Questionnaire (CBRSQ) was

239   developed to examine symptom specific unhelpful cognitive interpretations and related

240   coping strategies across different diseases (Loades et al., 2019; Moss-Morris & Chalder,

241   2003; Ryan et al., 2018; Skerrett & Moss-Morris, 2006). The scale was initially developed

242   and tested for reliability and validity and was found to be a reliable and valid measure of

243   coping responses (Loades et al., 2019).

244   **Table 1: A summary of self-report measures use to assess hypothesised mechanism of change in response to saMS CBT**

Self-report mediation measure used	How this measure relates to cognitive-behavioural factors drawn from Dennison et al's (2009) Model of Adjustment to MS	Psychometric properties of measures
Acceptance of Chronic Illness Questionnaire (Stuifbergen, Becker, Blozis, & Beal, 2008)	-Measures a person's ability to make use of psychological strategies in response to their MS by using acceptance and making adaptations.	-*Scale length: 14* items -*Item scoring:* 5-point Likert -*Scale meaning:* High scores on the scale indicate more illness acceptance (e.g. "I've come to terms with my MS" and associated adaptations to MS (e.g. "I can't conquer MS, but I can adapt to it." -*Scale scoring:* Sum items once appropriate items have been reverse scored
Psychological Vulnerability Scale (Sinclair & Wallston, 1999)	-Measures underlying beliefs relating to appraisal of self-worth and high personal expectations.	-*Scale length:* 6 items -*Item scoring:* 5-point Likert -*Scale meaning:* High scores on the scale indicate presence of unrealistic standards for oneself e.g. "I tend to set my goals too high and become frustrated trying to reach them" and a need to gain external approval from others e.g. "I need approval from others to feel good about myself" -*Scale scoring:* Sum items
Beliefs about Emotions Scale (Rimes & Chalder, 2010)	-Measures beliefs about the unacceptability of expressing and experiencing negative emotions.	-*Scale length:* 12 items but for this study an abbreviated six item scale was used including items: two, four, five, six, seven, and nine. These items were selected prior to the publication of 12-item scale because they represented a mix of content linked to both the expression and experience of negative

		emotions -*Item scoring:* 7-point Likert -*Scale meaning:* High scores on the scale represent a greater belief that it is unacceptable to express emotions e.g. "If I have difficulties I should not admit them to others" and experience negative thoughts and emotions "I should not let myself give in to negative feelings". -*Scale scoring:* Sum items
The below subscales from Cognitive-Behavioural Responses to Symptoms Questionnaire (Loades, Vitoratou, Rimes, Ali, & Chalder, 2019; Moss-Morris & Chalder, 2003; Ryan, Vitoratou, Goldsmith, & Chalder, 2018; Skerrett & Moss-Morris, 2006)		
Symptom focussing subscale	-Measures pwMS use of unhelpful cognitive coping strategies by focussing their attention on their physical symptoms	-*Total scale length:* 34 items -*Subscale length:* 6 items -*Item scoring:* 5-point Likert -*Scale meaning:* High scores indicates a person is paying a lot of attention to their physical symptoms e.g. "I worry when I am experiencing symptoms" -*Scale scoring:* Sum items once relevant items have been reverse scored
Catastrophising beliefs subscale from Cognitive Behavioural Responses to Symptoms Questionnaire	-Measures pwMS use of unhelpful cognitive appraisals in response to their symptoms or illness by predicting extreme or particularly negative outcomes.	-*Total scale length:* 34 items -*Subscale length:* 4 items -*Item scoring:* 5-point Likert -*Scale meaning: High scores indicates a person is more likely to predict the worse possible outcome for their symptoms and illness e.g.* "I worry that I may become permanently bedridden because of my symptoms",

		-Scale scoring: Sum items once relevant items have been reverse scored
Damage beliefs from Cognitive Behavioural Responses to Symptoms Questionnaire	-Measures pwMS beliefs that symptoms always indicate that further damage or harm is being done to their body.	*-Total scale length:* 34 items *-Subscale length:* 6 items *-Item scoring:* 5-point Likert *-Scale meaning:* High scores indicate that person believes that the presence of symptoms are a warning sign that harm is being caused e.g. "The severity of my symptoms must mean there is something serious going on in my body" *-Scale scoring:* Sum items once relevant items have been reverse scored
Fear Avoidance from Cognitive Behavioural Responses to Symptoms Questionnaire	-Measures pwMS use of unhelpful avoidance based coping strategies in response to fear of making symptoms worse.	*-Total scale length:* 34 items *-Subscale length:* 7 items *-Item scoring:* 5-point Likert *-Scale meaning: High scores indicate greater avoidance because of fear of exacerbating symptoms* e.g. "I am afraid that I will make my symptoms worse if I exercise" *-Scale scoring:* Sum items once relevant items have been reverse scored
Embarrassment Avoidance from Cognitive Behavioural Responses to Symptoms Questionnaire	-Measures pwMS tendency to avoid situations through feelings of embarrassment.	*-Total scale length:* 34 items *-Subscale length:* 6 items *-Item scoring:* 5-point Likert *-Scale meaning:* High scores indicates a person is more likely to withdraw from activities because of shame of fear of lack of control in public e.g. "I am embarrassed about my symptoms"

		-*Scale scoring:* Sum items once relevant items have been reverse scored
Resting/Limiting Behaviours from Cognitive Behavioural Responses to Symptoms Questionnaire	-Measures pwMS adaptive coping strategies by studying whether people engage in unhelpful periods of rest in response to their symptoms	-*Total scale length:* 34 items -*Subscale length:* 8 items -*Item scoring:* 5-point Likert -*Scale meaning:* High scores indicates a person reduces activities or rests in response to symptoms (e.g. I stay in bed to control my symptoms."). -*Scale scoring:* Sum items once relevant items have been reverse scored
All or nothing behaviours from Cognitive Behavioural Responses to Symptoms Questionnaire	-Measures whether pwMS engage in unhelpful periods of excessive activity which then have a negative impact, leading them to a period where they need to do nothing to rest and recover	-*Total scale length:* 34 items -*Subscale length: 5* items -*Item scoring:* 5-point Likert -*Scale meaning:* High scores indicates a person is engaging in excessive activity when symptoms are perceived to be less severe followed by periods of rest and recovery when symptoms exacerbate (e.g. "I tend to overdo things and then rest up for a while" -*Scale scoring:* Sum items once relevant items have been reverse scored

245

246   **Statistical Analysis**

247   Mediator and outcome variables and amount of missing data were summarised

248   using mean and standard deviation, or frequency and percentage, as appropriate. For

249   modelling, baseline and follow-up mediator and outcome variables were standardised to

250   baseline by subtracting the mean at baseline and dividing by the standard deviation (SD) at

251   baseline. Hence effect estimates are in baseline SD units, with the indirect/mediated effects

252   in baseline SD units of the outcome.

253

254   Readers are referred elsewhere for further details of mediation analysis (Goldsmith

255   et al., 2018a; Goldsmith et al., 2018b; MacKinnon & Luecken, 2008). Briefly, a model

256   following the structure shown in Figure 1 was fitted for each mediator, with the

257   independent variable dummy coded CBT versus SL, and using the post-treatment measure

258   of the mediator, with the 12-month follow-up measure of either GHQ (distress) or WSAS

259   (functional impairment) as the outcome. Using an earlier measure of the mediator and later

260   measure of the outcome respects the temporal hypothesis implicit in a mediation model

261   (Cole & Maxwell, 2003; Goldsmith et al., 2018a). Separate models were fitted for each

262   mediator of interest in combination with each outcome (simple mediator models, Figure 1).

263   Models were fitted in the structural equation modelling (SEM) framework, using full

264   information maximum likelihood and conditioning on covariates to account for missing data

265   under the missing at random assumption (Enders & Bandalos, 2001; Peters & Enders, 2002).

266   In practice, this meant each model fitted included all individuals. Adjustment for the

267   following potential confounders was made in all models by including all as covariates in both

268   the model for the mediator and the outcome: age, gender, severity of MS (measured using

269   the Expanded Disability Status Scale; EDSS (Kurtzke, 1983)), MS type coded as

270 relapsing/remitting or progressive, the baseline measure of the mediator and the baseline

271 measure of the outcome. Results were compiled for the *a* path, *b* path and the

272 indirect/mediated effect, which was calculated as *a* path x *b* path, or product of coefficients

273 estimate (MacKinnon, 2001). Percentile bootstrap 95% confidence intervals (CI) were

274 calculated for these effects, using 1000 repetitions, so p-values have not been provided. The

275 Mplus software, version 7, was used to fit the mediation SEM, with the R Mplus automation

276 package used to extract model results.

277   Given that the overall treatment effect was moderated, it was hypothesised that

278 there could be differing effects of CBT on the mediators based on baseline levels of distress

279 and that it was important to check for such mediated moderation (Muller et al., 2005). To

280 assess differing effects by baseline levels of distress, models were fitted as described above,

281 with the inclusion of a treatment by baseline distress interaction term in the equation for

282 the mediator (i.e. moderation of the *a* path). Note that in the case of the GHQ outcome,

283 rather than adjusting for baseline continuous GHQ, this analysis adjusted for the categorical

284 distress variable at baseline in equations for both the mediator and the outcome.

285

286   **Results**

287

288 **Data description and completeness**

289   The data completeness for all variables was good, with the greatest percentage

290 missing ranging between 5 – 7 % for post-treatment measures of the mediator. Summary

291 statistics for the mediator and outcome variables are shown in unadjusted mean profile

292 plots in Supplementary Materials - Appendix C Figures C1 and C2 and Supplementary

293 Materials- Appendix B Table B1 at the different pertinent time points.

294 **Does CBT have a significantly greater effect on the proposed mediators of change when**

295 **compared with SL?**

296

297   **Effect of saMS CBT as compared to SL on mediators at 15 weeks (a paths).**

298   In models with distress as the outcome, CBT led to a significantly greater decrease in

299 psychological vulnerability as compared to SL (-0.35, 95% CI -0.08 to -0.61, See Figure 3 and

300 Supplementary Materials Appendix B, Table B2). CBT also led to a greater decrease in

301 catastrophising (-0.34, 95% CI 0.004 to -0.65,), that didn't quite reach significance. For the

302 model with functional impairment as the outcome, CBT led to significantly greater

303 decreases in catastrophising (-0.36, 95% CI -0.02 to -0.65), psychological vulnerability (-0.30,

304 95% CI -0.02 to -0.570, and beliefs about emotions (-0.38, 95% CI -0.01 to -0.77). Note that

305 the *a* path estimates from the two models are similar but not exactly the same – the small

306 differences come from having fitted different SEMs for each outcome.

307

308 **Which of the putative mediators at the end of treatment are associated with**

309 **improvements in psychological distress and functional impairment at 12 months?**

310

311   **Effect of putative mediators on primary outcome general distress (*b* paths).**

312   There were significant relationships between embarrassment avoidance (0.28, 95%

313 CI 0.04 to 0.50, See Figure 4 and Supplementary Materials – Appendix B, Table B3) and fear

314 avoidance mediators (0.29, 95% CI 0.004 to 0.60) for the distress outcome. Interpreting

315 these from a traditional linear regression standpoint, these estimates suggest for every

316 baseline SD unit increase in embarrassment and fear avoidance post treatment, there was a

317 0.28 and 0.29 baseline SD increase in distress at 12 months follow-up, which is the direction

318   we expect for this relationship (and which implies that should the mediators be

319   decreased/improved by one baseline SD unit, we would see decreases/improvements of

320   these magnitudes in distress). There was also a significant relationship between acceptance

321   and distress, which as expected was in the opposite direction (as acceptance increased,

322   distress decreased indicating an improvement in distress symptoms by -0.30 baseline SD

323   units, 95% CI -0.01 to -0.62). It is of note that none of these mediators were significantly

324   affected by the CBT treatment – so at this point, we would not expect any significant

325   mediated effects.

326

327   **Effect of mediators on functional impairment outcome (*b* paths).**

328   There were significant relationships between acceptance of illness (-0.32, 95% CI -

329   0.08 to -0.60), beliefs about emotions (0.22, 95% CI 0.04 to 0.41) and embarrassment

330   avoidance (0.31, 95% CI 0.10 to 0.50) and the functional impairment outcome (See Figure 4

331   and Supplemental Materials B, Table B3), suggesting for every baseline SD unit increase in

332   acceptance of chronic illness post-treatment there was a 0.32 decrease in the degree of

333   perceived functional impairment at 12 months follow-up. In addition, for increases in beliefs

334   about emotions and embarrassment avoidance post treatment, there was a 0.22 and 0.31

335   baseline SD increase in functional impairment at 12 months. There was also a borderline

336   significant relationship between avoidance/resting behaviour and functional impairment

337   (0.34, baseline SD units, 95% CI 0.003 to 0.69). None of these mediators except for beliefs

338   about emotions were significantly affected by the CBT treatment, so the only mediator we

339   might expect significant mediated effects for would be beliefs about emotions.

340

341 **How much of the effect of CBT on outcomes (psychological distress and functional**

342 **impairment) is transmitted via the mediators in the total sample?**

343

344　　　　　**Mediated (Indirect) effect of treatment on distress and functional impairment via**

345　　　　　**mediators (a x b).**

346　　　　　There were no significant mediated effects for the distress outcome (See Figure 5

347 and Supplementary Materials Appendix B, Table B4). This follows from there being no

348 mediators affected by the treatment that also had a significant relationship with the distress

349 outcome. In other words, for some mediators the a path was significant, for different

350 mediators the b path was significant, but there were no examples where both were

351 significant, which would be needed for a significant mediated (indirect) effect.

352

353　　　　　Likewise, there were no significant mediated effects for the functional impairment

354 outcome (See Figure 5 and Supplementary Appendix B, Table B4).

355

356 **How much of the effect of CBT on outcomes is transmitted via the mediators in the groups**

357 **that were defined as clinically distressed at baseline versus not clinically distressed at**

358 **baseline?**

359

360　　　　　**Mediated moderation by baseline distress.**

361　　　　　A total of 56 individuals (60%) were classified as meeting criteria for clinical distress

362 at baseline. For both distress and functional impairment outcomes there were significantly

363 greater improvements in acceptance (e.g. levels of acceptance increased), beliefs about

364 emotions (e.g. perceiving it more acceptable to express emotions), embarrassment

365   avoidance (e.g. reducing avoidance related behaviours because of embarrassment) and

366   psychological vulnerability (e.g. lowered unrealistic standards and perceived need to please

367   others) (significant *a* paths) in those having CBT in the clinically distressed subset as

368   compared to SL, but no significant relationships were observed in the non- distressed group

369   (See Figures 6 and 7 and Supplementary Materials - Appendix B, Tables B5 and B7). There

370   was significant mediation of the effect of CBT on the distress outcome via acceptance and

371   embarrassment avoidance, with 0.20 and 0.22 baseline SD of the decrease in distress

372   transmitted via these mediators in the distressed subgroup (95% CI -0.01 to -0.46 and -0.02

373   to -0.58) (See Figure 6 and Supplementary Materials - Appendix B, Table B6). There was also

374   evidence for a significant mediated effect of CBT on the functional impairment outcome in

375   the clinically distressed group, with 0.19 baseline SD units of the effect transmitted via

376   beliefs about emotions (See Figure 7 and Supplementary Materials – Appendix B, Table B8,

377   95% CI -0.001 to -0.46). There was no evidence of mediation of treatment effects in the non-

378   distressed group.

379

380   **Conclusion**

381   **Summary of findings**

382   This study used mediation models to explore whether CBT significantly changed

383   selected key treatment mechanisms drawn from our original model of adjustment to MS

384   over time. Mediation models were used to determine if certain pre-defined mediators were

385   associated with distress and functional impairment. Mediated moderation analysis was

386   applied to explore how saMS CBT exerted its effect on both primary outcomes among pwMS

387   who had clinical levels of psychological distress as baseline.

388

389   When compared with SL, saMS CBT effectively changed some of the cognitive-

390   behavioural mechanisms (a paths) hypothesised to have an association with poor

391   psychological adjustment in MS. Specifically, pwMS who received saMS CBT had less critical

392   beliefs about the self as assessed using the psychological vulnerability scale, held fewer

393   catastrophic beliefs about MS, and held less negative beliefs about expressing negative

394   emotions at post treatment (15 weeks follow-up). However, when b paths were tested to

395   quantify whether the above three cognitive-behavioural mechanisms at end of treatment

396   (15 weeks) went on to have a downstream effect on outcomes at 12 months, no significant

397   relationships over time were observed. Therefore, the cognitive-behavioural mechanisms

398   which successfully changed in response to saMS CBT (a paths) were different from the

399   cognitive-behavioural mechanisms which had relationships with the primary outcomes over

400   time (b paths). Instead, four different cognitive-behavioural mechanisms of action showed

401   associations with the primary outcomes over time. Specifically, pwMS who were less

402   accepting of their MS and who were more likely to avoid situations because they felt

403   embarrassed reported higher levels of distress and functional impairment. In addition,

404   pwMS who feared that engaging in activities would make their symptoms worse at post-

405   treatment reported higher levels of distress at 12 months. Lastly, those who felt it was

406   inappropriate to express negative emotions at post treatment reported higher levels of

407   functional impairment at 12 months.

408

409   Although there was no evidence of mediation via hypothesised mechanistic

410   treatment pathways in the total sample, mediated moderation analyses showed that saMS

411   CBT was exerting its effects via some of these pathways for people with high baseline levels

412   of psychological distress. In comparison with SL, saMS CBT significantly changed levels of

413   acceptance and avoidance of activities due to feelings of embarrassment at post-treatment

414   in those with high baseline levels of distress. These two cognitive-behavioural mechanisms

415   of action then went on to have a beneficial downstream effect on distress at 12 months.

416   saMS CBT also significantly changed pwMS' unhelpful beliefs about processing negative

417   emotions at post-treatment in those with high distress, which in turn led to reductions in

418   functional impairment at 12 months.

419

420   **Interpretation of findings**

421

422   This study provided information on variables targeted by saMS CBT and which of

423   these potential mechanistic variables were associated with distress and functional

424   impairment. While the mechanisms of action responsible for the beneficial effect of saMS

425   CBT on psychological distress in the total sample of pwMS remains unclear (possibly

426   because the effect in the full sample was transmitted via unmeasured variables),

427   mechanisms were elucidated for the distressed subgroup at baseline. On a practical level,

428   there was no evidence of mediated treatment effects in the total sample because the

429   mechanisms affected by CBT (significant *a* paths) were different from the mechanisms

430   showing a downstream association with outcomes (significant *b* paths). This suggests if the

431   saMS treatment is to be used in a population including those with more minimal levels of

432   distress, aspects of the CBT manual may need to be refined to target outcome-associated

433   mechanisms (e.g. significant b paths).

434

435   Studying the *b* paths of the mediation analyses in more detail identified three

436   mechanisms of action likely to be important treatment targets for reducing psychological

437   distress. Specifically, this included acceptance, embarrassment avoidance, and fear

438   avoidance which all showed longitudinal associations with psychological distress but did not

439   change in response to saMS CBT in the total sample (e.g. *a paths* were statistically non-

440   significant). It may be that saMS CBT did not target these pathways with enough intensity to

441   bring about meaningful change. However, an alternative explanation for the lack of effect

442   of saMS CBT on these variables is that some of the sample at baseline were not experiencing

443   severe symptoms of psychological distress. As such, those with lower levels of distress may

444   have already accepted their MS and be less likely to be avoidant.   This latter explanation

445   may be more plausible given the mediated moderation analyses showed some of these

446   mechanisms (acceptance and embarrassment avoidance) were mediators of treatment

447   effects in people with clinical levels of distress at baseline.

448

449   When functional impairment was the outcome of interest, the mechanisms of action

450   that responded to CBT at post-treatment (*a* paths) were also different from the mechanisms

451   of action which showed downstream associations with functional impairment over time (*b*

452   paths) in the total sample. Consistent with the findings for distress, embarrassment

453   avoidance and acceptance at end of treatment predicted functional impairment at 12

454   months. In addition, resting or limiting activity in response to symptoms and feeling as

455   though it is unacceptable to express negative emotions also predicted functional

456   impairment at 12 months. As saMS CBT was multifactorial, it may be that focusing the

457   sessions more on these three mechanisms of change may enhance treatment effects when

458   attempting to improve functional impairment outcomes. It is noteworthy that reductions in

459   the belief that it is unacceptable to express negative emotions was a significant mediator of

460   improved functional impairment in the clinically distressed subgroup.

461 **Strengths and Limitations**

462 This is the first RCT of CBT for pwMS to perform a longitudinal mediation analysis

463 meeting some of the robust assumptions needed to infer causality (Cole & Maxwell, 2003;

464 Goldsmith et al., 2018a). In addition, the mechanisms of action selected for testing were

465 theoretically informed (Dennison et al., 2009) reducing the likelihood of type I errors. We

466 identified potentially salient updates to our theoretical model of adjustment and saMS CBT

467 manualised treatment protocol. Lastly, our statistical analyses controlled for potential

468 confounders, increasing confidence that the associations found were not subject to bias.

469

470 There were two key limitations of the study. First, its small sample size which likely

471 impacted on the statistical power to detect mediational mechanisms of action and likewise

472 the reliability of effect size estimates. This is particularly true for the mediated moderation

473 analysis. Indeed, the saMS RCT was statistically powered to perform an intention to treat

474 analysis on the study's primary outcomes but not its mediators and moderators. However,

475 to fully utilise available data and maximize statistical power we used robust maximum-

476 likelihood estimation procedures (Enders & Bandalos, 2001; Peters & Enders, 2002). Second,

477 the temporal measurement of distress and functional impairment at 12 months may have

478 been an inappropriate time lag to detect the effect of mediators on outcomes. Whilst lagged

479 mediator to outcome analyses meet causal assumptions (Cole & Maxwell, 2003; Goldsmith

480 et al., 2018b), relationships between this study's hypothesised mediators and study

481 outcomes may be contemporaneous or occur within a briefer timeframe; therefore the

482 opportunity to detect change may have been missed in this study (Cole & Maxwell, 2003;

483 Goldsmith et al., 2018a).

484

Implications and future work

The theoretical model of adjustment to MS (Dennison et al., 2009) already

emphasises the salient explanatory role of avoidance in the maintenance of poor

psychological adjustment to MS. This study's findings provide empirical support for these

mechanisms of action because associations were tested longitudinally.   The data suggest

that exploring avoidance in relation feelings of embarrassment and beliefs about symptoms

signifying damage may be particularly important. Studies of disorders such as chronic pain

focus on avoidance in terms of fear of activity (Crombez, Eccleston, Van Damme, Vlaeyen, &

Karoly, 2012). In MS, reasons for avoidance may be slightly different as highlighted by our

findings but these require replication. The findings highlight the potential for two other

explanatory mechanisms of action to feature more prominently in the model of adjustment

to MS. First, the role of acceptance and its relationship with both distress and functional

impairment needs further investigation. Second, the role of holding unhelpful beliefs about

negative emotions needs to be considered, particularly in relation to functional impairment.

Future iterations of saMS CBT could be tailored so that these mechanisms of action are

intensively targeted. Such strategies might include behavioural experiments and/or graded

exposure to address the unhelpful cognitions that are driving a person's patterns of

avoidance (Wells, 1997). The saMS CBT treatment protocol could also be updated to make

use of Acceptance and Commitment Therapy approaches so that pwMS are taught skills to

notice and accept distressing thoughts instead of searching for ways to control and

problem-solve areas that do not have a solution (McCracken, 2011).   It is worth noting that

although the selection of mediators in this study was theoretically informed by the model

of adjustment to MS (Dennison et al., 2009), we may have failed to measure some primary

509   mechanisms of change. For pragmatic reasons (i.e. measurement burden), we were not

510   able to measure all mechanisms of action that are cited in the model of adjustment to MS.

511   Qualitative interviews with 30 pwMS who took part in the saMS trial identified learning and

512   practicing skills to manage MS as core treatment components that pwMS valued (Dennison,

513   Moss-Morris, Yardley, Kirby, & Chalder, 2013). Therefore, it may be that improving MS

514   specific coping strategies are the mechanisms of action through which saMS CBT improves

515   distress outcomes, and future trials of saMS CBT should seek to test this hypothesis.

516

517   A particularly salient finding from both the original saMS RCT (Moss-Morris et al.,

518   2013) and this mediation analysis, is that results are strongest for pwMS with high baseline

519   levels of distress. This suggests patients could be screened for clinical distress when

520   attending for health care appointments. Given that health care systems are under

521   resourced, saMS CBT could be provided selectively to pwMS with high baseline levels of

522   distress, whilst less resource intensive self-management alternatives could be offered in the

523   first instance to those with less distress. This approach could also improve cost-effectiveness

524   of treatments for adjustment to MS, given that saMS CBT was not found to be a cost-

525   effective treatment in its current format (Mosweu, Moss-Morris, Dennison, Chalder, &

526   McCrone, 2017). Personalised psychological medicine, whereby the type of CBT intervention

527   approaches offered to pwMS are mapped to their baseline adjustment profile may further

528   improve outcomes and health care efficiencies. Indeed, a review of psychological

529   treatments delivered in the UK found that when mental health services recorded a person's

530   primary presenting problem at assessment better health outcomes were observed because

531   it allowed the selection and implementation of evidence-based treatment protocols tailored

532   to the specific needs of patients (Clark et al., 2017).

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533

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541

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548

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551   Dr. Hudson reports personal fees from Consultancy work for Mahana Therapeutics, other;

552   from a private company who signed a license agreement with King's College London with the view to

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556

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575   other from a private company who signed a license agreement with King's College London with the

576   view to bringing a website CBT intervention for irritable bowel syndrome product to the NHS and

577   other international markets, outside the submitted work.

578

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699

700

Figure 3. Treatment – mediator *a* paths

[INSERT FIGURE 3 HERE]

GHQ = general health questionnaire 12 outcome, WSA = work and social adjustment outcome. AVOID = behaviour

avoidance subscale of the CBRSQ, ACHC = acceptance of chronic health conditions scale, ALL NOTH = all or nothing

subscale of the CBRSQ, BES = beliefs about emotions scale, CAT = catastrophising subscale of the CBRSQ, DAM BEH =

damage behaviour subscale of the CBRSQ , EMB AV = embarrassment avoidance subscale of the CBRSQ, FEAR AV = fear

avoidance subscale of the CBRSQ, PVS = psychological vulnerability scale, SYM FOC = symptom focusing subscale of the

CBRSQ. 95% confidence intervals that exclude the dotted reference line at zero indicate a statistically significant estimate.

Figure 4. Mediator – Outcome *b* paths

[INSERT FIGURE 4 HERE]

GHQ = general health questionnaire 12 outcome, WSA = work and social adjustment outcome. AVOID = behaviour avoidance subscale of the CBRSQ, ACHC = acceptance of chronic health conditions scale, ALL NOTH = all or nothing subscale of the CBRSQ, BES = beliefs about emotions scale, CAT = catastrophising subscale of the CBRSQ, DAM BEH = damage behaviour subscale of the CBRSQ , EMB AV = embarrassment avoidance subscale of the CBRSQ, FEAR AV = fear avoidance subscale of the CBRSQ, PVS = psychological vulnerability scale, SYM FOC = symptom focusing subscale of the CBRSQ. 95% confidence intervals that exclude the dotted reference line at zero indicate a statistically significant estimate.

Figure 5. Indirect (mediated) effects of treatment on distress via mediators

[INSERT FIGURE 5 HERE]

GHQ = general health questionnaire 12 outcome, WSA = work and social adjustment outcome. AVOID = behaviour

avoidance subscale of the CBRSQ, ACHC = acceptance of chronic health conditions scale, ALL NOTH = all or nothing

subscale of the CBRSQ, BES = beliefs about emotions scale, CAT = catastrophising subscale of the CBRSQ, DAM BEH =

damage behaviour subscale of the CBRSQ , EMB AV = embarrassment avoidance subscale of the CBRSQ, FEAR AV = fear

avoidance subscale of the CBRSQ, PVS = psychological vulnerability scale, SYM FOC = symptom focusing subscale of the

CBRSQ. 95% confidence intervals that exclude the dotted reference line at zero indicate a statistically significant estimate.

Figure 6. Distress moderated *a* paths and indirect effects for distress outcome

[INSERT FIGURE 6 HERE]

ACHC = acceptance of chronic health conditions scale, BES = beliefs about emotions scale, EMB AV = embarrassment

avoidance subscale of the CBRSQ, PVS = psychological vulnerability scale. 95% confidence intervals that exclude the dotted

reference line at zero indicate a statistically significant estimate.
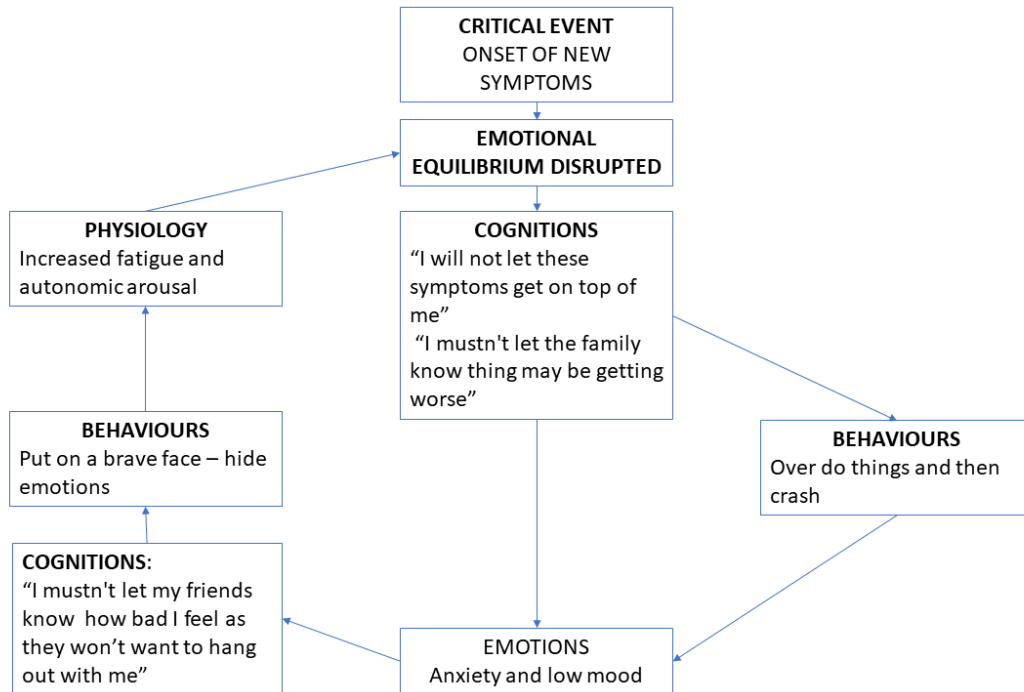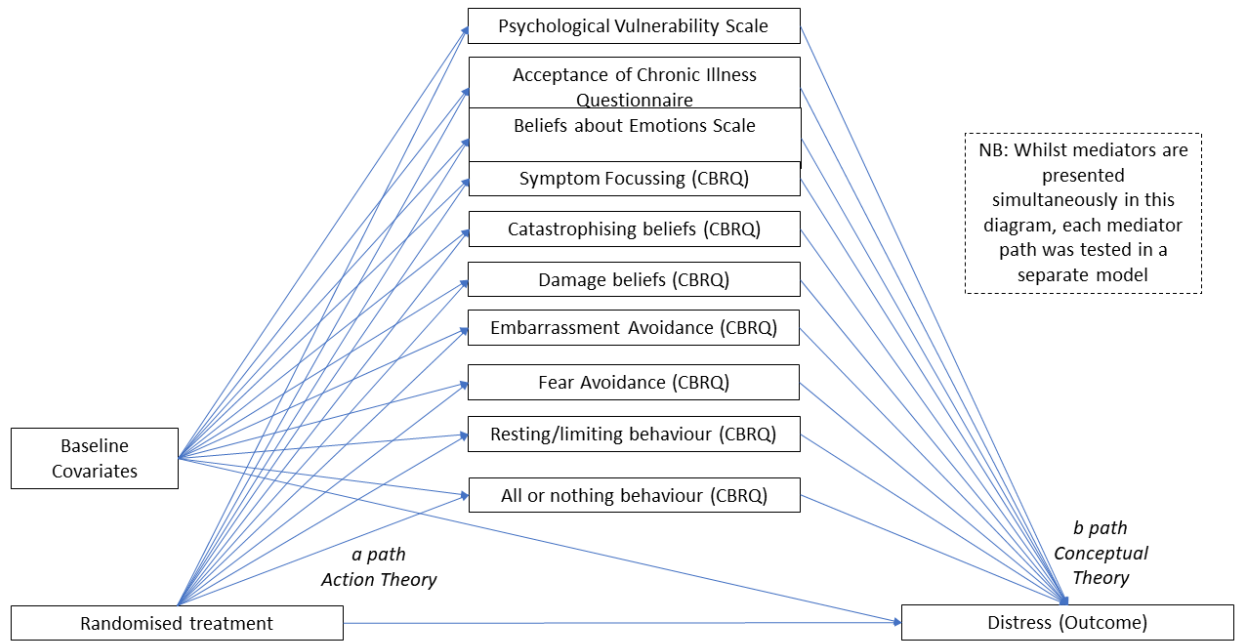
Figure 7. Distress moderated *a* paths and indirect effects for functional impairment outcome
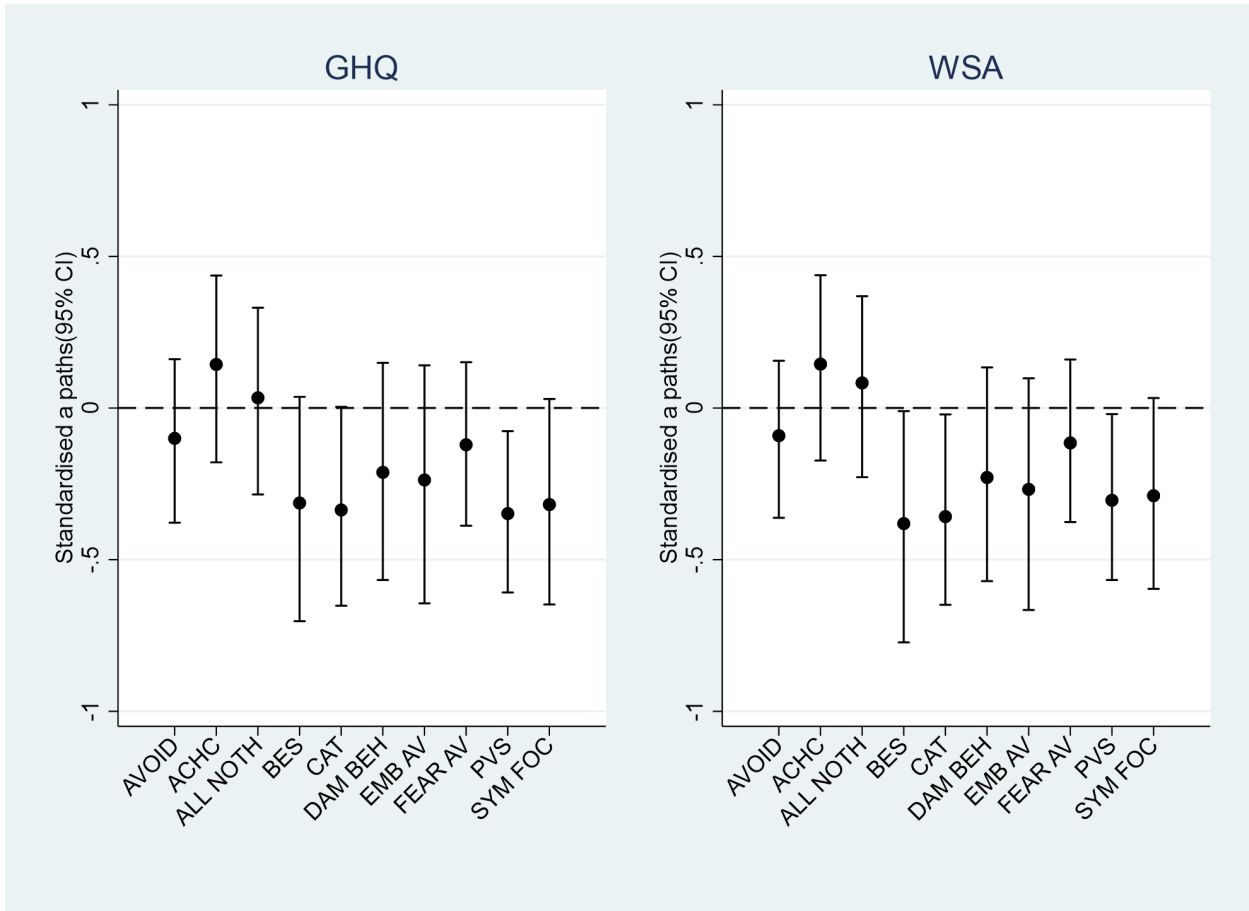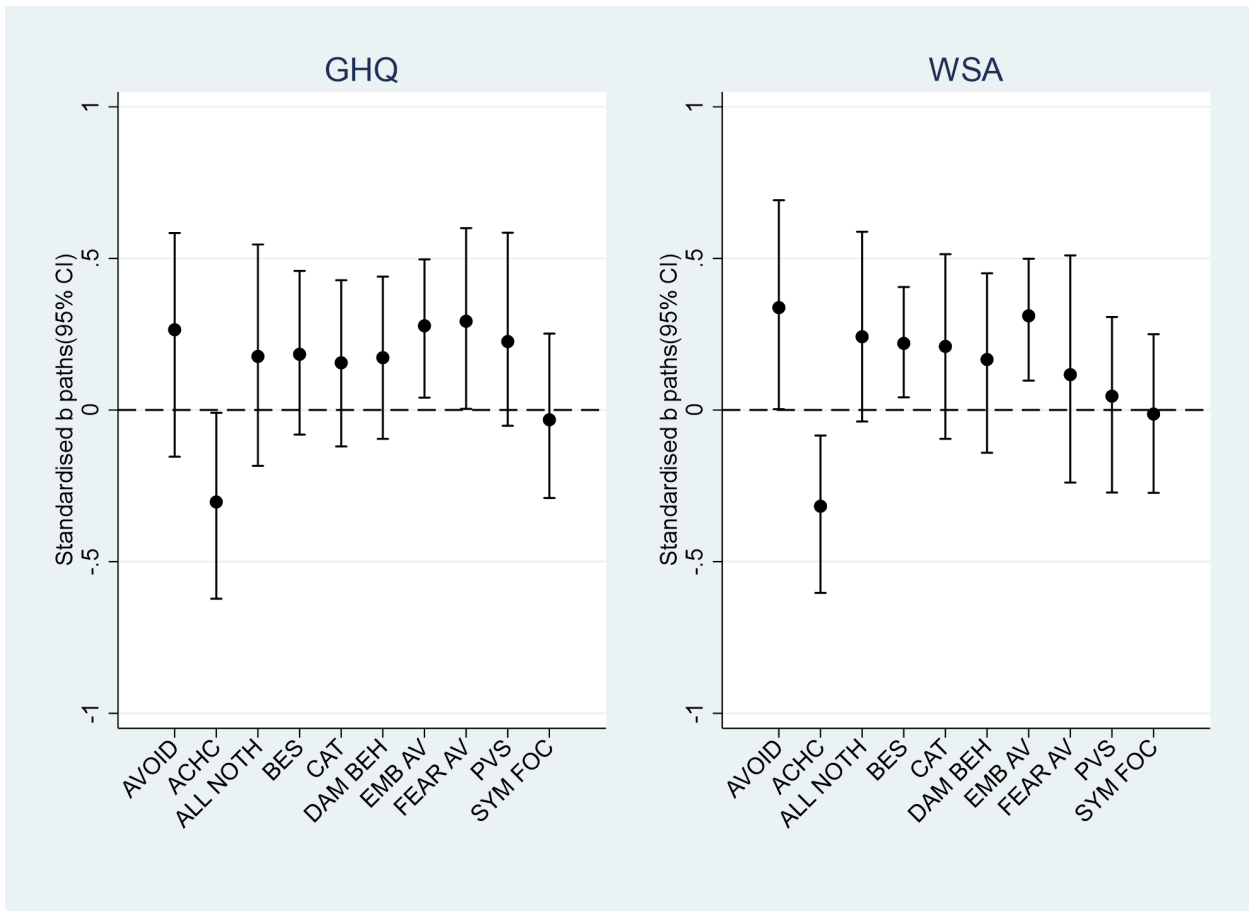
[INSERT FIGURE 7 HERE]

ACHC = acceptance of chronic health conditions scale, BES = beliefs about emotions scale, EMB AV = embarrassment

avoidance subscale of the CBRSQ, PVS = psychological vulnerability scale. 95% confidence intervals that exclude the dotted

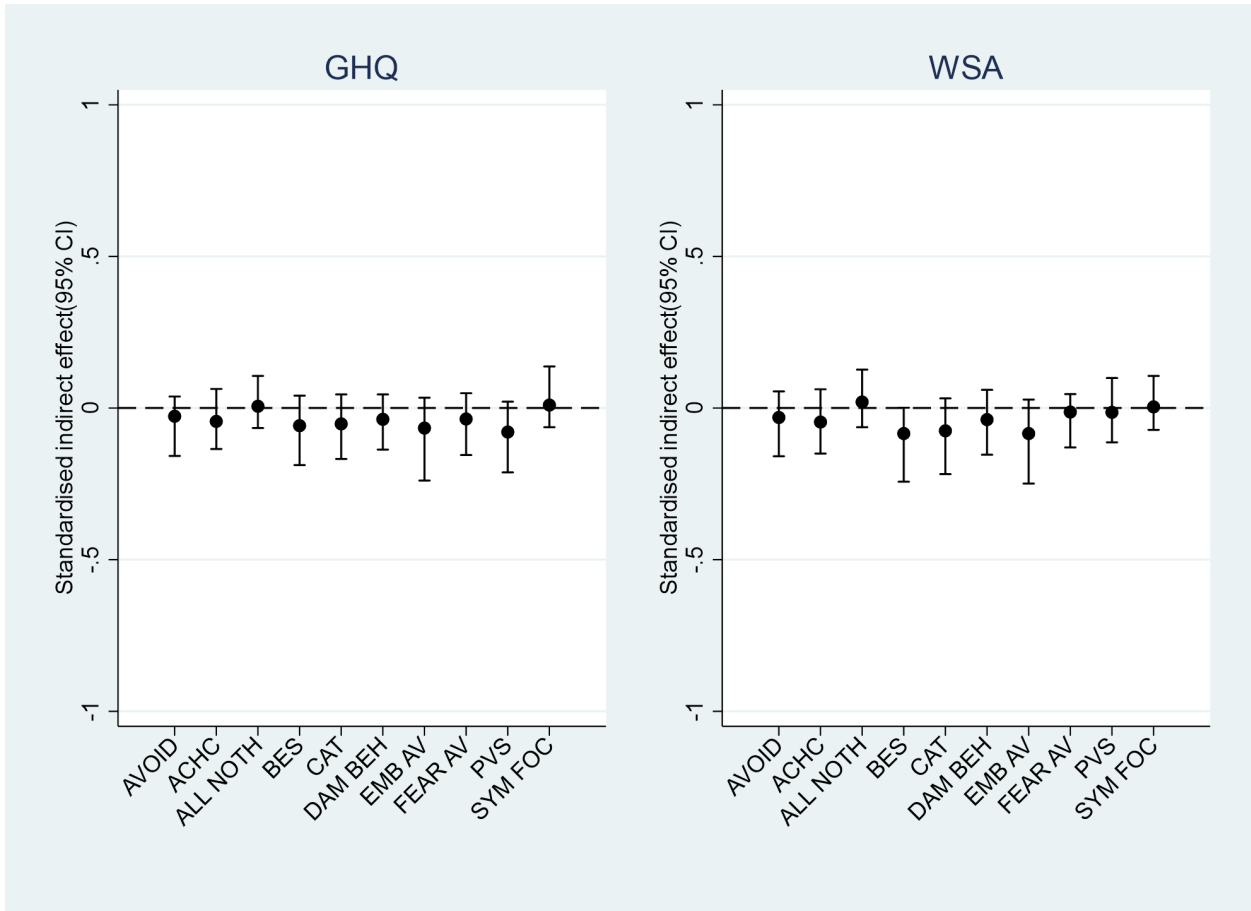reference line at zero indicate a statistically significant estimate.

CRITICAL EVENT
ONSET OF NEW
SYMPTOMS

EMOTIONAL
EQUILIBRIUM DISRUPTED

PHYSIOLOGY
Increased fatigue and
autonomic arousal

COGNITIONS
"I will not let these
symptoms get on top of
me"
"I mustn't let the family
know thing may be getting
worse"

BEHAVIOURS
Put on a brave face – hide
emotions

BEHAVIOURS
Over do things and then
crash

COGNITIONS:
"I mustn't let my friends
know how bad I feel as
they won't want to hang
out with me"

EMOTIONS
Anxiety and low mood

Psychological Vulnerability Scale

Acceptance of Chronic Illness Questionnaire

Beliefs about Emotions Scale

Symptom Focussing (CBRQ)

Catastrophising beliefs (CBRQ)

Damage beliefs (CBRQ)

Embarrassment Avoidance (CBRQ)

Fear Avoidance (CBRQ)

Resting/limiting behaviour (CBRQ)

All or nothing behaviour (CBRQ)

NB: Whilst mediators are presented simultaneously in this diagram, each mediator path was tested in a separate model

Baseline Covariates

Randomised treatment

a path
Action Theory

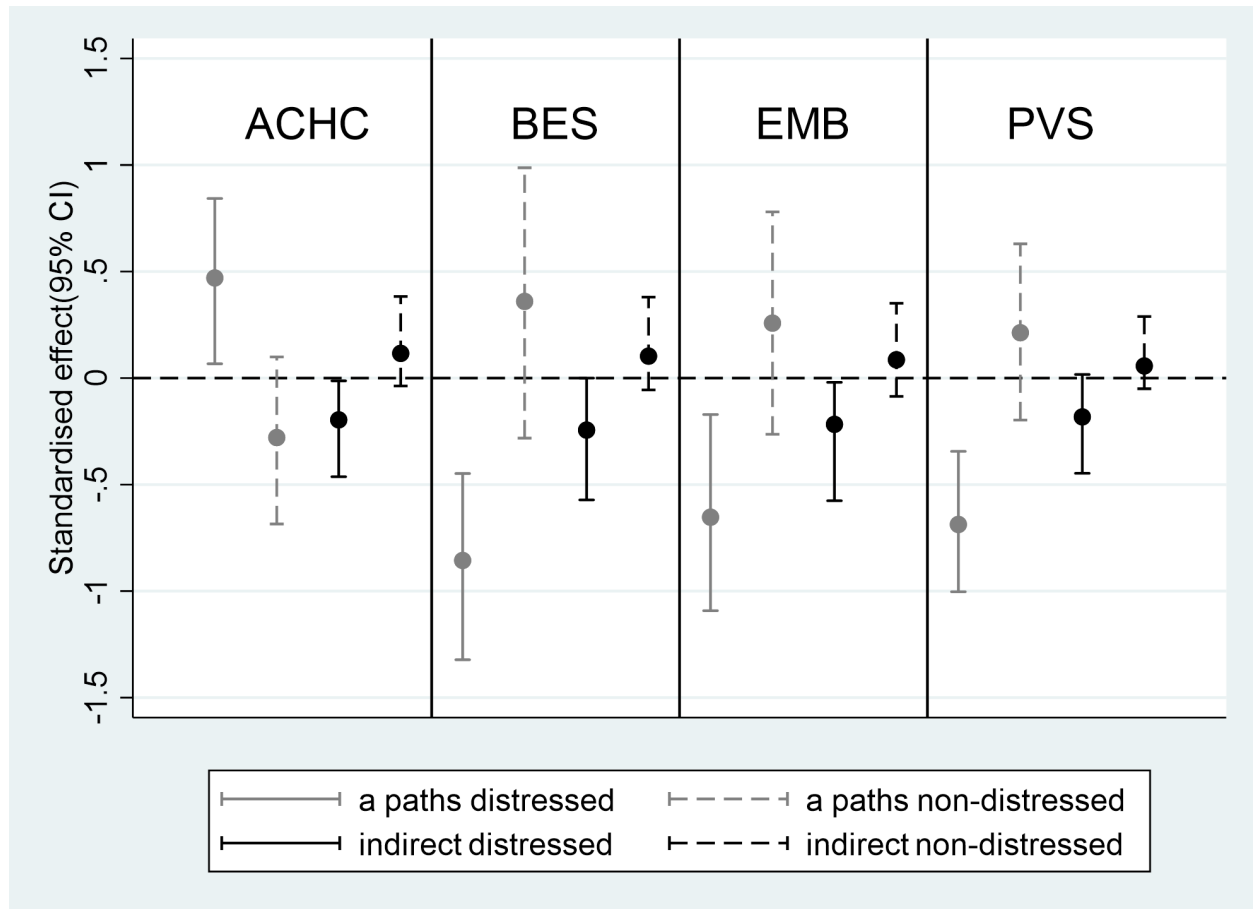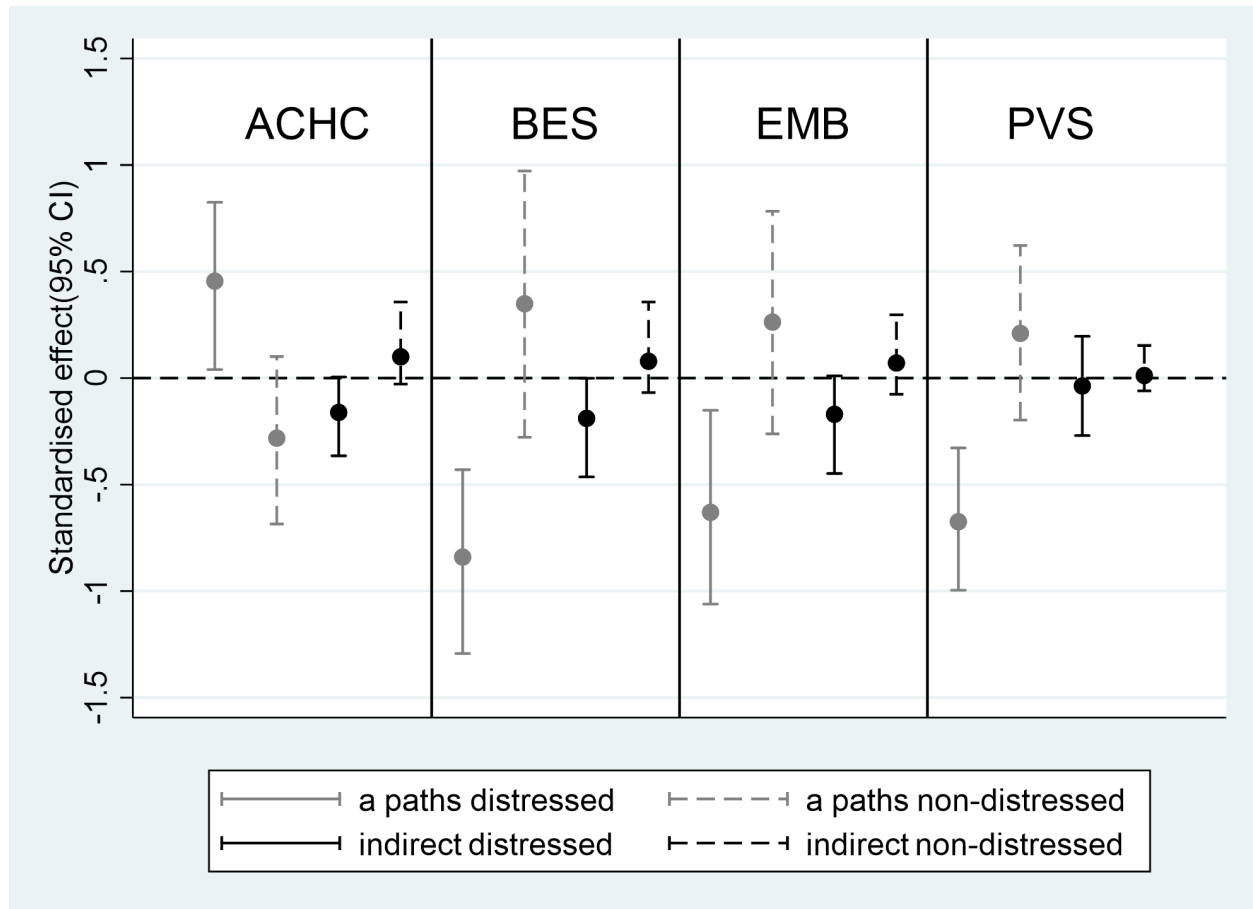*b path*
Conceptual Theory

Distress (Outcome)

Highlights:

- Cognitive behavioural therapy (CBT) improves distress in multiple sclerosis (MS).
- How and for whom CBT works in the MS population is unknown.
- Mediation and mediated-moderation analyses of randomised controlled trial data were conducted.
- CBT for MS improved distress and functioning via hypothesised mechanisms of action.
- However, mediation occurred only for those with clinical distress at baseline.